AMENDMENTS TO THE SPECIFICATION

Delete existing Figures 4A, 4B, and 5 and insert the replacement formal drawings (Figures 4A, 4B, and 5).

At page 7, line 30, amend table 1 as follows:

Lys(N(epsilon)-trifluoracetyl)	-	~~kTFA]~~ k(TFA)

Amend the paragraph at page 20, line 1, as follows:

Table 3. Illustration of the design of the conformation determining regions and protease binding sites in molecules having P domains larger that 4 amino acids. The P1 residue is underlined. Z is benzyloxycarbonyl group, ~~K[TFA]~~ K(TFA) means Lys(N(epsilon)trifluoroacetyl), is Fmoc (preferably attached to the alpha amino group of the amino terminal residue *e.,g.*, Lysine (K). O indicates tetrahydroisoquinoline-3-carboxylic acid. Aib, designated as B, can be replaced by Pro.

Delete Table 3 at page 20 and insert the following:

Name	aa^1	aa^2-aa^3	aa^4	aa^5	X	P	Y	aa^6	aa^7	aa^8-aa^9	aa^{10}	S^2
PAI-2	Lys	Asp		Aib		Thr Gly Arg Thr Gly		Pro			Lys	GlyTyr
PAI-2(b)	Lys	Asp	Pro	Pro		Thr Gly Arg Thr Gly		Pro	Pro		Lys	GlyTyr
DEVD	Lys	Asp		Aib		Asp Glu Val Asp Gly Ile Asp		Pro			Lys	GlyTyr
DevN	Lys	Asp		Aib		Asp Glu Val Asn Gly Ile Asp		Pro			Lys	GlyTyr
PARP	Lys	Asp		Aib		Glu Val Asp Gly Ile Asp		Pro			Lys	GlyTyr
ICE	Lys	AspTyr		Aib		Ala Asp Gly Ile Asp		Pro			Lys	GlyTyr
Fm-DEVD	Fm-Lys	Asp		Aib		Asp Glu Val Asp Gly Ile Asp		Pro			Lys	GlyTyr
Fm-	Fm-	Asp		Aib		Asp Glu Val		Pro			Lys	GlyTyr

DEVN	Lys					Asn Gly Ile Asp						
Fm-PARP	Fm-Lys	Asp		Aib		Glu Val Asp Gly Ile Asp		Pro			Lys	GlyTyr
Fm-KNFES	Fm-Lys	Asp		-		Ala Ile Pro Met Ser Ile		Pro			Lys	GlyTyr
	Fm-Lys	Asp				Ala Ile Pro Nlu Ser Ile		Pro			Lys	GlyTyr
Fm-G2D2D	Fm-Lys	Asp		Aib		Gly Asp Glu Val Asp Gly Ile Asp	Gly	Pro			Lys	GlyTyr
Fm-CGD2D	Fm-Lys	Asp		Aib	Ahx	Gly Asp Glu Val Asp Gly Ile Asp	GlyAhx	Pro			Lys	GlyTyr
Z-CGD2D	Z-Lys	Asp		Aib	Ahx	Gly Asp Glu Val Asp Gly Ile Asp	GlyAhx	Pro			Lys	GlyTyr
Fm-ICE	Fm-Lys	AspTyr		Aib		Ala Asp Gly Ile Asp		Pro			Lys	GlyTyr

Amend the paragraph at page 21, line 1, as follows:

Table 4. Illustration of the design of the conformation determining regions and protease binding sites in molecules having P domains larger that 4 amino acids. The P1 residue is underlined. Z is benzyloxycarbonyl group, ~~K[TFA]~~ K(TFA)means Lys(N(epsilon)trifluoroacetyl), Fm is Fmoc (preferably attached to the alpha amino group of the amino terminal residue *e.,g.*, Lysine (K). O indicates tetrahydroisoquinoline-3-carboxylic acid. Aib, designated as B, can be replaced by Pro. J is a C

Amend the paragraph at page 52, lines 13-20 as follows:

Fluorophores were linked to the amino terminus via the α-amino group of aspartic acid residue (D) and to the ε-amino group of lysine (K). Labeling was accomplished by the displacement of a succinimidyl group linked to 6-TMR or DER. The structure of the peptide, called NorFES-KGY is:

~~**Fluorophore1-DAIPNleSIPKGY**~~

~~**Fluorophore2**~~

Q5 conclude

Fluorophore1-AspAlaIl ProNleS rIleProLysGlyTyr

Fluorophore2

(SEQ ID NO: 181).

Delete Table 12 at pages 55-56 and insert the following:

Q6

	Structure	Cellular uptake/ magnitude	Uptake checked by	Seq ID NO
1	Fm-Lys(F1) Asp Ala Ile Pro Nlu Ser Ile Pro Lys (F1) Gly Tyr	Yes/high	FM	182
2	Lys(F1) Asp Ala Ile Pro Nlu Ser Ile Pro Lys (F1) Gly Tyr	Yes/weak	FM	183
3	Fm-Asp Ala Ile Pro Nlu Ser Ile Pro Lys (F1)Gly Tyr	No/	FM	184
4	Fm-Lys (F1) Asp Aib Asp Glu Val Asp Gly Ile Asp Pro Lys (F1) Gly Tyr	Yes/high	FM & FC	185
5	Lys (F1) Asp Aib Asp Glu Val Asp Gly Ile Asp Pro Lys (F1) Gly Tyr	Yes/weak	FM	186
6	Fm-Lys (F1) Asp Aib Asp Glu Val Ile Nlu Gly Ile Asp Pro Lys (F1) Gly Tyr	Yes/high	FM	188
7	Lys (F1) Asp Aib Asp Glu Val Nlu Gly Ile Asp Pro Lys (F1) Gly Tyr	Yes/weak	FM & H	188
8	Fm-Lys(F1) Asp Aib Glu Val AspGlyIleAspProLys(F1)GlyTyr	Yes/high	FM & FC	189
9	Lys (F1) Asp Tyr Aib Ala Asp Gly Ile Asp Pro Lys (F1) Gly Tyr	Yes/weak	FM	190
10	Fm-Lys (F1) Asp Aib Gly Asp Glu Val Asp Gly Ile Asp Gly Pro Lys (F1) Gly Tyr	Yes/high	H & FC	191
11	Fm-Lys(F1) Asp Aib Ahx Gly Asp Glu Val Asp Gly Ile Asp Gly Ahx Pro Lys(F1)Gly Tyr	Yes/high	FC	192
12	Z-Lys (F1) Asp Aib Ahx Gly Asp Glu Val Asp Gly Ile Asp Gly Ahx Pro Lys (F1) Gly Tyr	Yes/weak	FM	193

13	Fm-Lys (F1) Asp Tyr Aib Ala Asp Gly Ile Asp Pro Lys (F1) Gly Tyr	Yes/high	FM	194
14	Lys (F1) Asp Aib Glu Val Asp Gly Ile Asp Pro Lys (F1) Gly Tyr	Yes/weak	FM	195

Amend the paragraph at page 55, lines 7-15 as follows:

In addition, we have synthesized and derivatized (homodoubly-labeled) PAI-2, CS-1 (a 31 residue long peptide) and two DEVD-like peptides that did not allow the dye-dye dimer formation. The CS-1 peptide shows that in a significantly longer peptide the dye-dye dimer structure can be formed. Note this peptide contains four proline residues in the amino terminal side of the putative cleavage site Ile-Leu bond. There is one proline in the carboxyl domain also. The results from the CS-1 peptide support a potentially larger sequence between the two dyes (fluorophores). Two DEVD-like peptide's amino acid sequences that did not allow the formation of productive H-type dimers are F_1-~~DEVDGIDPK[F_1]GY and F_1-PDEVDGIDPK[F_1]GY~~. AspGluValAspGlyIleAspProLys(F_1)GlyTyr and Pro AspGluValAspGlyIleAspProLys(F_1)GlyTyr.

Amend the paragraph at page 57, lines 10-21, as follows:

The elastase substrate, ~~Fm-K[F1]DAIPNluSIPK[F1]GY~~ Fm-Lys(F1)AspAlaIleProNluSerIleProLys(F1)GlyTyr, (SEQ ID NO:196, where F1 was carboxytetramethylrhodamine, Fm was Fmoc, ~~K[F1]~~ K(F1)was F1 covalently attached through the epsilon amino group of lysine (K), and Fm-K is the Fmoc group covalently attached at the alpha amino group of the amino terminal lysine residue) was used with HL-60 cells. Cells were incubated with various concentrations of elastase substrate ranging from 10 nM to 10 μM for 5 minutes to 60 minutes. Then the cells were diluted 5-fold with RPMI 1640 medium containing 5% serum or with phosphate buffered saline. The samples were centrifuged and washed once more with 1 ml of washing solution. After centrifugation and removal of the washing solution, cell pellets were loosened with about 25 ul of medium and these cells were transferred to a glass capillary. Capillary tubes were then placed on a glass microscope slide and examined under a fluorescence microscope using standard rhodamine filters.

Amend the paragraph at page 58, lines 6-23, as follows:

09

Control cells without substrate incubation and the sample with the greatest expected fluorescence signals were used to set the instrument detector parameters. For example after 15 minutes incubation of Jurkat cells with substrate compound #11 Fm-CGD2D: Fm-CGD2D: ~~Fm-K[F1]DBJGDEVDGIDGJPK[F1]GY-~~Fm-Lys(F1)AspAibAhxGlyAspGluValAspGlyIleAspGlyAhxProLys(F1)GlyTyr (SEQ ID NO:197, where F1 was carboxytetramethylrhodamine; Fm was Fmoc, ~~K[F1]~~ K(F1) was F1 covalently attached through the epsilon amino group of lysine (K), Nlu was norleucine, B was aminoisobutyric acid, and J was epsilon-aminocaproic acid) an increase of about 10 channels indicating cellular uptake of the substrates was measured. Note substrate #11 was not completely quenched. Hence, a small amount of background fluorescence would be expected from the intact substrate. Signals from the cells that had been activated with 1 ug/ml of ant-Fas antibody, CH11 clone for 1 to 6 hours indicated an increase in peak channel number. As much as a ten-fold increase in fluorescence intensity was observed. When the cells were co-incubated with the CPP32 protease inhibitor ZVAD-fluoromethylketone at 50 μM along with an apoptosis inducing agent, *e.g.,* anti-Fas antibody, this observed increase in fluorescence intensity was eliminated. This indicated that the signal from compound 11 was due to the CPP32 protease activity which was inhibitable by ZVAD-FMK. Hence, the observed fluorescence intensity in each cell as determined by flow cytometric analysis served as a direct measure of the intracellular CPP32 protease activity.

Amend the paragraph at page 59, lines 18-27, as follows:

010

Jurkat cells are normally grown in 10% fetal calf serum containing RPMI 1640, at 37° C in a 5% CO_2 atmosphere. When the serum content was dropped to 4%, the Jurkat cell growth rate not only slowed down but also a significant number of cells died within 36 hours. The cell density used was about 400,000 cell per ml. After 36 hours, control wells contained about 50% dead cells (trypan blue-positive cells), whereas the wells containing 0.1 or 1.0 μM concentration of compound #11 (Table 12) "Fm-CGD2D" or ~~Fm-K[F1]DBJGDEVDGIDGJPK[F1]GY-~~Fm-Lys(F1)AspAibAhxGlyAspGluValAspGlyIleAspGlyAhxProLys(F1)GlyTyr (SEQ ID NO:198) showed only 10% or 8% nonviable cells. Hence, compound #11 which exhibits efficient cellular

uptake slowed down apoptosis in these Jurkat cells where it acted as a CPP32 protease inhibitor or a CPP32 activating protease inhibitor.

Amend the paragraph at page 61, lines 26 through page 62, line 156 as follows:

The parent compound Fm-DEVD has the following composition: ~~Fmoc-K[F1]DBDEVDGIDPK[F1]GY-~~ Fmoc-Lys(F1)AspAibAspGluValGlyIleAspProLys(F1)GlyTyr (SEQ ID NO:199). The bold face underlined letters are the protease recognition sequence consisting of 7 amino acid residues. Compound #10 contains two glycine extensions at both ends of this protease recognition sequence. The central protease recognition domain now is 8 residues long ~~GDEVDGID~~ GlyAspGluValAspGlyIleAsp(SEQ ID NO:200), since the glycine residue at the amino terminus is a part of native sequence. The two glycine residues which are inherently more flexible than other amino acids, *e.g.,* alanine, provide less conformational constraint or, conversely, more flexibility than compound 4 (Table 12) and thereby permit greater flexion when combined with Aib or Pro residues. Additional insertion of amino caproic acid at both termini with five methylene groups in addition to the one present in glycine provides further relaxation of the constrained conformation and, thus, greater flexibility for the protease recognition domain, ~~GDEVDGID~~ GlyAspGluValAspGlyIleAsp (SEQ ID NO:200). This progression of flexibility resulted in an increased hydrolysis rate with the CPP32 protease since CPP32 recognizes a more flexible protease recognition domain than does elastase. Support for this statement is that the CPP32 protease cleavage site in the proform of its physiological substrate, poly(ADP-ribose) polymerase, PARP, is located between two well-folded domains. Hence, it is expected that such a protease cleavage site would not be rigidly held or its conformation would be expected to be less defined than the remaining molecule. Hence, in order to provide these structural features to the substrate, introduction of flexible residues such as glycine, epsilon amino caproic acid, beta alanine, and amino butyric acid would be expected to play important roles in regulating the backbone flexibility of the substrate=s central protease recognition domain. These additional preferred residues for the conformation determining domain are also expected to provide the needed bend-inducing influence.

Amend the paragraphs at page 62, lines 23-34 as follows:

These examples provide a tetrapeptide and a pentapeptide comprising Lys-Asp-Aib-Gly (SEQ ID NO:201) or Lys-Asp-Aib-Ahx-Gly (SEQ ID NO:202) where Ahx is episilon amino caproic acid (*i.e.* NH_2-$(CH_2)_5$-COOH). The fluorophore is attached to episilon amino group of the lysine residue. The carboxyl terminal CDR domain is defined as a tripeptide Gly-Pro-Lys and a tetrapeptide Gly-Ahx-Pro-Lys (SEQ ID NO:203). The hydrolysis rate was increased by 3-fold between compounds 4 (Fm-DEVD: ~~Fm-K[F1]DBDEVDGIDPK[F1]GY~~ Fm-Lys(F1)AspAibAspGluValAspGlyIleAspProLys(F1)GlyTyr, (SEQ ID NO:204) and 10 (Fm-G2D2D: ~~Fm-Lys(F1)DBGDEVDGIDGPK[F1]GY~~ Fm-Lys(F1)AspAibAspGluValAspGlyIleAspProLys(F1)GlyTyr, SEQ ID NO:205)

As illustrated in Figure 5, the hydrolysis rate was further increased by *ca.* 3-fold over the above glycine residue insertion with the amino caproic amino acid (Ahx) addition, compound 11 (Fm-CGD2D: ~~Fm-K[F1]DB-Ahx-GDEVDGIDG-Ahx-PK[F1]GY~~ Fm-Lys(F1)Asp Aib Ahx Gly Asp Glu Val Asp Gly Ile Asp Gly Ahx Pro Lys (F1) Gly Tyr, SEQ ID NO:206). Hence, overall at least a 9-fold increase in substrate hydrolysis rate was accomplished (compounds 4 and 11, Table 12).

Delete Table 4 at pages 21-29 and insert the accompanying replacement Table 4.